

September 17, 1965

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Dear Al:

The protocol "Convulsive Therapy and Electroencephalographic Change" interested me very much and I found much in the protocol to commend it for study. Rather than describe some generalities, perhaps the best I can do is to comment on each of the sections and then make some general overview comments at the end.

The introduction and specific aims are quite clear and I would concur that such a study is needed. The specific aims on page 2 are clear for a and b. Aim c is a specific reflection of Dr. Marshall's interests, but he should be prepared to defend this since to my knowledge there are no studies which have suggested that the seizure pattern during a convulsion is significantly different either depending on type of induction nor in terms of the therapeutic result. There are some reports suggesting that there are changes in the threshold to induced convulsions and that these threshold changes are related to clinical improvement. However, to ask this question would require considerable effort in anesthetizing patients to the same degree of anesthesia and then determining the threshold for convulsion each treatment. While this has been done for electroconvulsive induction, I wonder if this is a reasonable suggestion for Indoklon.

Aims d and f are redundant. Aim e is a good one but the phrase "process electroencephalographic records" is unclear to me. Do you mean the EEG records during each treatment?

Since the purpose of the program is to relate EEG changes and behavioral response, and you are focussing on some predictors, perhaps you would consider an additional aim to determine predictors of neurophysiological response. I do not know if I have sent you a copy of a paper that was never published in which we related some of the pre-treatment EEG characteristics and certain psychological test performances to the amount of induced slow wave activity.

However, since you are measuring slow wave activity and will be doing psychological tests, and determining the EEG characteristics in the pre-treatment record, perhaps such a substudy would complement this project.

The treatment plan is also sufficiently clear. However, in the prediction of treatment response, there are significant differences in the predictions in depressives and in schizophrenic subjects. The rate of slow wave induction in depressives is generally higher than in schizophrenic; and the behavioral adaptations to these brain changes is different depending on the pre-treatment personality of the subject. In our studies we tended to disregard the differences between schizophrenics and depressives and I believe this has hurt our analyses. By providing that you will be studying both depressives and schizophrenics it may be important to indicate that the analyses should be done separately before the two groups with the anticipation that relationships between induced slow wave activity and clinical result may be found in group and not in the other.

On page three the treatment paragraph brings in a new topic which is not related to the aims of the study program. There is little evidence that the two methods of induction are different with regard to the amount of slow wave activity induced. Perhaps an additional aim should be specified to determine if the method of induction does bear any relationship to the amount of EEG change and to the treatment result.

While the number of treatments (9-15) is adequate, in certain schizophrenic patients the amount of slow wave activity induced on a three times a week schedule may not be sufficient to have a significant behavioral response. We have noted frequently that such patients require more than 15 treatments and that often it may be necessary to increase the rate from three to five times a week. Perhaps a disclaimer could be entered into the treatment paragraph indicating that if, after 15 individual treatments, the amount of slow wave activity is less than 20% or 30%, the patient will receive an additional number of treatments so that he has 20 and perhaps even 25.

The inclusion of a three week post-treatment study period is excellent. However, the evidence is fairly clear that this may not be long enough. Later on in the protocol you indicate a six week period and this is much better. (Some studies have shown that the amount of slow wave activity disappears quickly, but we have observed patients in whom slowing ~~is~~ still present as long as three months after treatment. Equally important is the development of long runs and high percent time alpha activity which often replaces the pre-treatment disorganized or desynchronized records.)

On page four the evaluations appear to be adequate. The psychometric assessments imply that you are going to reassess the role of ~~cognitive~~ disorganization and memory change. The relation between cognitive disorganization and memory loss to treatment response has been studied extensively and there is considerable evidence that memory changes are often seen in patients who favorably respond, but that the usual memory tests are too insensitive to show changes in brain function. When these tests have been applied by sophisticated observers like those in Sweden, the relationships have been well documented. For this reason, I am not clear as to why so much effort will be expended in this direction. However, I would like to make two specific suggestions which can augment this battery. In our studies we were very much impressed that the amount of slow wave activity was related to certain pre-treatment psychological characteristics of the patients. The two tests that were most important were the hidden figures test and the California F-Scale. Performance on these tests was related to the amount of induced slowing. However, more important from the point of view of therapeutic response, the California F-Scale seemed related to the clinical behavioral response. The other psychological tests did not show such a relationship. However, Dr. Kahn had developed a denial personality inventory and this, when applied to the patients behavior prior to treatment, was highly predictive of the behavioral evaluation. We did not find this related to the amount of EEG change, however.

Thus, depending on the amount of effort you wish to make in psychometric assessments, the goals should be clarified and perhaps two sets of tasks included; those which may be related to the amount of slow wave activity and those that may be related to improvement.

With regards to the EEG records, the section on baseline EEG is excellent. Page five, section 2, brings up the focus of the study once again. Previous studies have shown that the amount of slow wave activity which may be related to therapeutic response is the amount of slowing found between treatment sessions. It is the early development and maintenance of high voltage slow wave activity which has been shown to be related to therapeutic response. By emphasizing the EEG during the treatment itself, it will be difficult to develop any parallels with other studies except during the post-treatment period. At one time we attempted to measure the EEG changes immediately post-seizure and to relate these to the treatment outcome. In many patients for periods up to one hour we found continuous low voltage one to three cycle per second activity which was correlated with the extent of post-seizure confusion and disorientation. When these patients were recalled 4 to 6 hours later, the amount of delta activity was often very little, showing that the patient had a very active homeostatic mechanism and that the induced slow wave activity disappeared quickly. For this reason

in our studies we took our EEG record 24 to 32 hours after an induced convulsion. (Seizures were given on Monday, Wednesday and Friday, and all EEGs were taken on Tuesday, Thursday, or Saturday.) To relate the present study to previous studies, I believe records should be taken during the interseizure period, and during the treatment course as well.

Section 3 on page five is excellent and I would urge you to attempt weekly records up to six weeks minimum.

Page six technique is fine.

Data analysis is unclear. If the purpose of the study program is to corroborate earlier observations, then perhaps the methods used should be spelled out and described to indicate that you are willing to undertake such confirmation. If the techniques are new ones and I believe that this is what you would prefer, then the quantitative methods should be described in sufficient detail. Nowhere in this outline nor in the supplementary letter from Dr. Marshall is the technique of analysis described except the visual. Now, I believe the visual is more than adequate to accomplish the missions assigned. However, if the recording on magnetic tape and subsequent quantitative analysis is to be done, then these methods should be spelled out. In view of the present status of EEG analysis, I wonder why you have not considered one of the analog analytic systems. There are two excellent ones, the power spectral density using Grey-Walters original filter model and the period analysis. Equipment for both is commercially available and while the Grey Walter system will not give you frequencies below 3 cps with any fidelity, the period analytic programs will. In either case, the reviewing group will be very critical of such a paragraph on data analysis.

From Dr. Marshall's letter, I imagine he is considering the eventual use of digital computers for the analysis of these tapes. If that is so, then these methods should be described in greater detail. Our studies are now being written in a form suitable for presentation but we have described three different digital analytic programs: the power spectral density analysis, period analysis, and a random shapes model. These analytic methods are expensive but we are now analyzing tapes sent to us from Dr. Denber. If the volume of tapes provided by your laboratories is not too great, we can, starting next summer, analyze some of your tapes and provide you with frequency spectra and period analytic spectra at different stages for any or all of the lead combinations you may select. I would recommend that you include a paragraph in your application stating that if you are given an opportunity to collect tapes, that these may be analyzed by me assuming that this facility is still operational at that time. (We are now summarizing the programs that we have worked on these past three years and will ourselves go to NIH for additional support late this winter, as our grant support ends October 1, 1966.)

Returning to page six, section a, the descriptions provided by Dr. Marshall are excellent, even though I would argue with the use of the word "abnormal". Somehow, the development of slow wave activity in a post-seizure record is the normal effect of such seizures and very much to be desired. The use of the word "abnormal" has a negative connotation which prejudices an observers view of these changes.

The section b on page seven is satisfactory since Dr. Marshall has been identified with such analyses in the past.

Section c, page seven, can be criticized only as I did earlier. The ten minutes following the post-ictal depression is not going to be sufficient for the study that you envisage. I think this paragraph should be rewritten after you have considered the need for interseizure records.

On page eight, the suggestion that "the relative amount of this slow activity after each convulsive treatment will be examined for its utility as a regulating index for further treatment" is a good suggestion. However, from my own experience, I believe that the interseizure record will probably be more helpful. However, both may be done.

The section d on page eight is very important and may provide a special focus of your study. I would like to suggest that this paragraph not emphasize the reappearance of the individuals pre-treatment brain potentials, for this is highly unlikely. What is often seen is the development of increased rhythmicity, higher percent time alpha, and increased voltages which persist for many weeks to months. In those patients who fail the treatment and who regress quickly, this rhythmicity is often lacking. A focus on this period of time may be very valuable.

The significance paragraph is good and I would suggest a few additions. In the first paragraph the issue is the relationship between the amount of delta activity in the EEG both during a series of convulsive treatments and after. It seems to me that the significance should emphasize the psychological and behavioral tests which you are including. I would urge that the significance encompass such statements that some observers have indicated that slow wave activity is an outward sign that biochemical changes of the brain have been induced and that these changes are persistent in some patients and not in others. When these changes persist, then the likelihood of improvement is high especially in patients who have had a depressive disorder and in whom the denial personality is permanent. In those patients in whom these changes disappear quickly or in whom they fail to appear, the biochemical changes in the brain are too weak to induce behavioral change or are transient. The personality and psychological factors which may be related both to the induction of high voltage slow wave activity and behavioral improvement of a persistent variety will be studied in this program.

The paragraph regarding tape recordings is not part of significance but rather part of the justification for special equipment.

Reviewing Dr. Marshall's letter, my comments follow the comments on the original grant application.

The justification for an ampex DAS-100 is not made clear. I believe that if you were to ask for analog equipment to analyze tapes or to analyze on-going records this would be highly commendable. To record tapes in the quantity that you have requested is also a commendable suggestion, but for this I think his comments on page two are sufficient. The multichannel memory device as a Nuclear Chicago RIDL is too small for the operations which you envisage and this is probably not to be considered. With regard to tape recording, the use of an SP-300 even with 7 channels costs about \$10,000 and this should be included in your request, especially if you decide to include the possibility of having tapes analyzed by my facility. You should be prepared, however, to indicate that the present program outlined includes 21 tapes per patient and that if both treatment procedures are to be carried out with approximately 30 subjects in each cell, then a minimum of ~~500~~ 2400 tapes will be needed and since Dr. Marshall indicates that he would like these as a library, the investment is approximately ~~\$20,000~~ \$20,000.

I have no criticism of the use of krohn-hite filters for these are helpful for visual analysis. However, I think an analog analytic system is probably to be preferred although you may still wish to use filters for preprocessing.

In reviewing the application there a number of things which are omitted and these are largely in the clinical area. I think you should suggest the numbers of subjects to be considered and the rate at which you think you can bring them into your program from your facility. Perhaps one should focus a little more clearly on the decision making process regarding number of treatments because this will effect the analysis of the post-treatment EEGs. Setting nine treatments as a minimum is satisfactory, for depressives but not for schizophrenics. In either case, however, the criterion for clinical judgement should be described as either memory changes, or behavioral improvement with resolution of certain symptoms or the development of a denial syndrome.

As I review these notes, the program is a good one and I would be pleased to see it undertaken.

As I read these notes, I am indeed sorry that I did not have an opportunity to visit with you because much could be clarified in a conference situation. Nevertheless, I hope these comments are helpful.

Dr. Kurland

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September 17, 1965

I will send them out this afternoon and then call you early in the week so that we can discuss this on the telephone.

My best regards.

Sincerely yours,

Max Fink, M.D.
Professor of Psychiatry

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